



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 1 344 525 A1

(12) EUROPEAN PATENT APPLICATION
published in accordance with Art. 158(3) EPC

(43) Date of publication:
17.09.2003 Bulletin 2003/38

(51) Int Cl. 7: A61K 31/44, A61K 31/505

(21) Application number: 01271863.1

(86) International application number:
PCT/JP01/11282

(22) Date of filing: 21.12.2001

(87) International publication number:
WO 02/051397 (04.07.2002 Gazette 2002/27)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

- KIMURA, Hirohiko,
c/o Ishihara Sangyo Kaisha, Ltd.
Kusatsu-shi, Shiga 525-0025 (JP)
- YUKI, Shunji, c/o Ishihara Sangyo Kaisha, Ltd.
Kusatsu-shi, Shiga 525-0025 (JP)
- YAMAMOTO, Kazuhiro, c/o Ishihara Sangyo
Kaisha, Ltd
Kusa tsu-shi, Shiga 525-0025 (JP)
- OKADA, Takashi,
c/o Ishihara Sangyo Kaisha, Ltd.
Kusatsu-shi, Shiga 525-0025 (JP)

(30) Priority: 22.12.2000 JP 2000391175

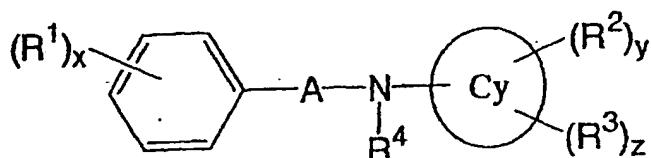
(74) Representative: Dendorfer, Claus, Dr. et al
Wächtershäuser & Hartz
Tal 29
80331 München (DE)

(71) Applicant: ISHIHARA SANGYO KAISHA, LTD.
Nishi-ku, Osaka 550-0002 (JP)

(72) Inventors:
• KATO, Fuminori,
c/o Ishihara Sangyo Kaisha, Ltd.
Kusatsu-shi, Shiga 525-0025 (JP)

(54) ANILINE DERIVATIVES OR SALTS THEREOF AND CYTOKINE PRODUCTION INHIBITORS
CONTAINING THE SAME

(57) The present invention provides a cytokine production inhibitor containing as an active ingredient an aniline derivative of the formula (I) or a salt thereof:



[wherein A is CO or SO₂; Cy is an aryl group or a heterocyclic group; each of R¹ and R² which are independent of each other, is a halogen atom, a cyano group, a nitro group, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted, a heterocyclic group which may be substituted, an amino group which may be substituted or a -B-Q group; R³ is a -M¹-M²-R⁵ group; R⁴ is a hydrogen atom or an alkyl group which may be substituted; x is an integer of from 0 to 5; y is an integer of from 0 to 4; and z is an integer of from 0 to 1].

EP 1 344 525 A1

Description**TECHNICAL FIELD**

5 [0001] The present invention relates to aniline derivatives or salts thereof, and cytokine production inhibitors containing the same as an active ingredient. The cytokine production inhibitors of the present invention are useful as preventive or therapeutic medicines for diseases accompanied by hyperactivated immune functions, such as allergic diseases, systemic autoimmune diseases and organ specific autoimmune diseases, or as preventive or therapeutic medicines for graft rejection in organ transplantation.

10 **BACKGROUND ART**

[0002] In immune reactions in the body, cytokines produced from various immunocytes control direction of the immune responses. In this regulation of immune responses, it is helper T cells that play a central role, and they are classified into subsets Th1 and Th2 depending upon the type of cytokines they produce. Th1 type cells are known to produce mainly e.g. interleukin 2 (IL-2) and interferon γ (IFN- γ) and to be concerned with cellular immunity such as protection of infection against e.g. virus and bacteria. Th2 type cells are known to produce mainly e.g. interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 10 (IL-10) and interleukin 13 (IL-13) and to be concerned with humoral immunity such as protection of infection against parasites and antibody production from B cells. However, it has been clarified that if control of such biophylactic mechanism dysfunctions or deteriorates for some reason, hyperactivation or imbalance of immune function may occur, thus inducing or deteriorating various diseases.

[0003] Immune response of Th2 type induces or activates, due to its hyperactivation, allergic inflammation reactions such as immediate type allergy with which IgE antibody or mast cells are mainly concerned, and delayed-type allergy with which eosinophils are mainly concerned, and is deeply concerned with induction or deterioration of various allergic diseases such as urticaria, food allergy, anaphylactic shock, hypereosinophilic syndrome, asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis. Further, abnormal hyperactivation of immune reaction of Th2 type is deeply concerned also with systemic autoimmune diseases in a pathophysiologic state where antibody production or humoral immunity is hyperactivated, such as systemic lupus erythematosus. It is considered to be important to control the immune response of Th2 type in order to treat or prevent such allergic diseases. On the other hand, immune response of Th1 type induces or activates cellular immune responses due to its hyperactivation, and is deeply concerned with induction or deterioration of organ specific autoimmune diseases such as chronic rheumatoid arthritis, type I diabetes, Hashimoto's thyroiditis, myasthenia gravis and multiple sclerosis. Further, cellular immune response of Th1 type is deeply concerned also with graft rejection accompanying organ transplantation. It is considered to be important to control immune response of Th1 type in order to prevent or treat such autoimmune diseases or graft rejection after transplantation.

[0004] As compounds which are analogous in chemical structures to the aniline derivative or a salt thereof as an active ingredient of the cytokine production inhibitors of the present invention, compounds as disclosed in WO95/146, WO98/27081 WO98/27058 WO99/15164, WO99/51580 and WO00/40235 may, for example, be mentioned. However, such compounds and the compounds of the present invention are different in their chemical structures.

[0005] At the present time, it is difficult to treat such serious immune or allergic diseases by specifically regulating immune response of Th1 or Th2 type, and immunosuppressant agents which strongly suppress production of both Th1 and Th2 type cytokines, such as cyclosporin and FK506, in addition to steroids, are mainly used as therapeutic medicines for such diseases. However, various side effects such as dysfunction of adrenal cortex, diabetes, peptic ulcer and glaucoma have been problematic with respect to steroids, and serious side effects such as damages in kidney and central nervous system have been problematic with respect to cyclosporin and FK506, and development of a new type of cytokine production inhibitors which are different from the above agents, has been desired.

DISCLOSURE OF THE INVENTION

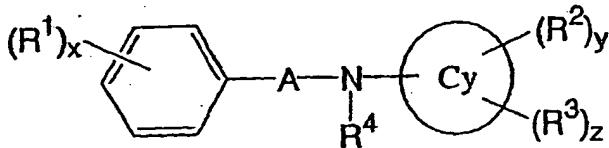
50 [0006] The present inventors have found that aniline derivatives having chemical structures which are totally different from those of active ingredients in existing agents have cytokine production inhibitory effects, and the present invention has been accomplished on the basis of this discovery. The aniline derivatives suppress production of Th2 type cytokine, whereby they are useful as preventive or therapeutic medicines for various allergic diseases such as urticaria, food allergy, anaphylactic shock, hypereosinophilic syndrome, asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis; and systemic autoimmune diseases in which antibody production or humoral immunity is hyperactivated, such as systemic lupus erythematosus. Further, they suppress production of Th1 type cytokine, whereby they are useful as preventive or therapeutic medicines for organ specific autoimmune diseases such as chronic rheumatoid arthritis, type I diabetes, Hashimoto's thyroiditis, myasthenia gravis and multiple sclerosis; and graft rejection accompanying organ

transplantation.

[0007] The present inventors have conducted extensive studies to find more excellent cytokine production inhibitors and as a result, have accomplished the present invention. Namely, the present invention relates to a cytokine production inhibitor containing as an active ingredient an aniline derivative of the formula (I) or a salt thereof:

5

10



[0007] [wherein A is CO or SO₂; Cy is an aryl group or a heterocyclic group; each of R¹ and R² which are independent of each other, is a halogen atom, a cyano group, a nitro group, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted, a heterocyclic group which may be substituted, an amino group which may be substituted or a -B-Q group (wherein B is O, CO, COO, OCO, S, SO or SO₂; and Q is a hydrogen atom, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted, a heterocyclic group which may be substituted or an amino group which may be substituted); R³ is a -M¹-M²-R⁵ group (wherein each of M¹ and M² which are independent of each other, is O, S, a NR⁶ group (wherein R⁶ is a hydrogen atom or an alkyl group which may be substituted), a single bond, a C₁₋₂ alkylene chain, CO, SO or SO₂, or M¹ and M² together may form -N=N-; and R⁵ is a cycloalkyl group which may be substituted, an aryl group which may be substituted or a heterocyclic group which may be substituted); R⁴ is a hydrogen atom or an alkyl group which may be substituted; x is an integer of from 0 to 5; y is an integer of from 0 to 4; and z is an integer of from 0 to 1; provided that (1) a case where Cy is a phenyl group, and the substituent at the 4-position of the phenyl group is a pyrazole group which may be substituted or a triazole group which may be substituted, and (2) a case where Cy is a phenyl group, the substituent at the 2-position of the phenyl group is an alkyl group, and the substituent at the 5-position is a -NHCO-(CH₂)^q-R group (wherein q is an integer of from 1 to 4, and R is an aryl group or a cycloalkyl group) are excluded].

[0008] The salt of the aniline derivative of the above formula (I) may be any pharmaceutically acceptable salt, and it may, for example, be a mineral acid salt such as a hydrochloride, a sulfate or a nitrate; an organic acid salt such as a p-toluenesulfonate, a propane sulfonate or a methane sulfonate; an alkali metal salt such as a potassium salt or a sodium salt; an alkaline earth metal salt such as a calcium salt; or an organic amine salt such as a triethanol amine salt or a tris(hydroxymethyl)aminomethane salt. Some of these salts have crystal water.

[0009] Each of the alkyl group which may be substituted represented by each of R¹, R², R⁴, R⁶ and Q, and the alkyl moiety in each of the secondary substituent and the tertiary substituent as described hereinafter, may be usually one having a carbon number of from 1 to 18, and it may, for example, be a methyl group, an ethyl group, a propyl group, a butyl group, a pentyl group, a hexyl group, a heptyl group, an octyl group, a decyl group or a nonadecyl group, and they include linear or branched aliphatic structural isomers.

[0010] Each of the alkenyl group which may be substituted represented by each of R¹, R² and Q, and the alkenyl moiety in each of the secondary substituent and the tertiary substituent as described hereinafter, may be usually one having a carbon number of from 2 to 18, and it may, for example, be a vinyl group, a propenyl group, a butenyl group, a pentenyl group, a hexenyl group, a decenyl group or a nonadecenyl group, and they include linear or branched aliphatic structural isomers.

[0011] Each of the alkynyl group which may be substituted represented by each of R¹, R² and Q, and the alkynyl moiety in each of the secondary substituent and the tertiary substituent as described hereinafter, may be usually one having a carbon number of from 2 to 18, and it may, for example, be an ethynyl group, a propynyl group, a butynyl group, a pentynyl group, a hexynyl group, a decynyl group or a nonadecynyl group, and they include linear or branched aliphatic structural isomers.

[0012] Each of the cycloalkyl group which may be substituted represented by each of R¹, R², R⁵ and Q and the cycloalkyl moiety in each of the secondary substituent and the tertiary substituent as described hereinafter, may be usually one having a carbon number of from 3 to 10, and it may, for example, be a monocyclic group such as a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group or a cyclooctyl group; a fused-polycyclic group; or a crosslinked polycyclic group such as an adamantyl group, a noradamantyl group, a norbornanyl group or a norbornanonyl group.

[0013] Each of the cycloalkenyl group which may be substituted represented by each of R¹, R² and Q and the cycloalkenyl moiety in each of the secondary substituent and the tertiary substituent as described hereinafter, may be usually one having a carbon number of from 3 to 10, and it may, for example, be a monocyclic group such as a cyclopentenyl group, a cyclohexenyl group or a cyclooctenyl group, a fused-polycyclic group or a crosslinked polycyclic

group.
[0014] Each of the aryl group which may be substituted represented by each of R¹, R², R⁵ and Q, the aryl group represented by Cy and the aryl moiety in each of the secondary substituent and the tertiary substituent as described hereinafter, may be a fused-polycyclic group such as a naphthyl group, as well as a phenyl group.

[0015] Each of the heterocyclic group which may be substituted represented by each of R¹, R², R⁵ and Q, the heterocyclic group represented by Cy and the heterocyclic moiety in each of the secondary substituent and the tertiary

a pyrimidyl group, a dihydropyrimidyl group, a tetrahydropyrimidyl group, a hexahydropyrimidyl group, a pyridazinyl group, a dihydropyridazinyl group, a tetrahydropyridazinyl group, a hexahydropyridazinyl group, a pyrazinyl group, a dihydropyrazinyl group, a tertahydropyrazinyl group, a piperazinyl group, a triazinyl group, a dihydrotriazinyl group, a tetrahydrotriazinyl group, a hexahydrotriazinyl group, a pyranyl group, a dihydropyranyl group, a tetrahydropyranyl group, a dioxinyl group, a dioxyenyl group, a dioxanyl group, a dithianyl group or a morpholinyl group; a fused-polycyclic heterocyclic group such as a thienothienyl group, a dihydrocyclopentathienyl group, an indolyl group, a tetrahydroindolyl group, an isoindolyl group, a tetrahydroisoindolyl group, a benzothienyl group, a tetrahydrobenzothienyl group, a benzofuranyl group, a tetrahydrobenzofuranyl group, a benzoxazolyl group, a tetrahydrobenzoxazolyl group, a benzisoxazolyl group, a tetrahydrobenzisoxazolyl group, a benzothiazolyl group, a tetrahydrobenzothiazolyl group, a benzothiazolyl group, a tetrahydrobenzothiazolyl group, a benzimidazolyl group, a tetrahydrobenzimidazolyl group, a benzodioxolyl group, a benzodithioliyl group, a benzodioxanyl group, a benzodithianyl group, a quolinolyl group, an isoquinolinyl group, a quinazolinyl group, a quinoxalinyl group, a phthalazinyl group, a naphthyridinyl group or a purinyl group or a crosslinked polycyclic heterocyclic group such as a quinuclidinyl group.

[0016] The secondary substituent of each of the alkyl group which may be substituted, the alkenyl group which may be substituted and the alkynyl group which may be substituted, may, for example, be a halogen atom, a hydroxyl group, a mercapto group, an alkoxy group, a substitutable alkylthio group, a substitutable alkenyloxy group, a substitutable alkenylthio group, a substitutable alkynyoxy group, a substitutable alkynylthio group, a substitutable cycloalkyl group, a substitutable cycloalkenyl group, a substitutable cycloalkoxy group, a substitutable cycloalkylthio group, a substitutable cycloalkenylthio group, a substitutable cycloalkenylthio group, a substitutable alkoxycarbonyl group, a substitutable alkylcarbonyl group, a substitutable alkylcarbonyloxy group, a substitutable alkenyloxycarbonyl group, a substitutable alkenylcarbonyl group, a substitutable alkenylcarbonyloxy group, a substitutable alkynyoxy carbonyl group, a substitutable alkynylcarbonyl group, a substitutable alkynylcarbonyloxy group, a substitutable cycloalkoxycarbonyl group, a substitutable cycloalkylcarbonyl group, a substitutable cycloalkylcarbonyloxy group, a substitutable cycloalkenyl group, a substitutable cycloalkenylcarbonyl group, a substitutable cycloalkenylcarbonyloxy group, a substitutable aryl group, a substitutable aryloxy group, a substitutable arylthio group, a substitutable aryloxycarbonyl group, a substitutable arylcarbonyl group, a substitutable arylcarbonyloxy group, a substitutable heterocyclic group, a substitutable heterocyclyloxy group, a substitutable heterocyclylthio group, a substitutable heterocyclyloxycarbonyl group, a substitutable heterocyclylcarbonyl group, a substitutable heterocyclylcarbonyloxy group, a substitutable amino group, a cyano group, a nitro group, a carboxyl group, a substitutable aminocarbonyl group, a substitutable alkylsulfonyl group, a substitutable alkenylsulfonyl group, a substitutable alkynylsulfonyl group, a substitutable cycloalkylsulfonyl group, a substitutable cycloalkenylsulfonyl group, a substitutable arylsulfonyl group, a substitutable heterocyclylsulfonyl group or a substitutable aminosulfonyl group. The number of such substituents may be one or two or more, and such substituents may be the same or different.

[0017] The secondary substituent of each of the cycloalkyl group which may be substituted, the cycloalkenyl group which may be substituted, the aryl group which may be substituted and the heterocyclic group which may be substituted, may, for example, be a halogen atom, a hydroxyl group, a mercapto group, a substitutable alkyl group, a substitutable alkenyl group, a substitutable alkynyl group, a substitutable alkoxy group, a substitutable alkylthio group, a substitutable alkenyloxy group, a substitutable alkenylthio group, a substitutable alkynyoxy group, a substitutable alkynylthio group,

a substitutable cycloalkyl group, a substitutable cycloalkenyl group, a substitutable cycloalkoxy group, a substitutable cycloalkylthio group, a substitutable cycloalkyloxy group, a substitutable cycloalkenylthio group, a substitutable alkoxy carbonyl group, a substitutable alkyl carbonyl group, a substitutable alkyl carbonyloxy group, a substitutable alkenyloxy carbonyl group, a substitutable alkenyl carbonyl group, a substitutable alkenyl carbonyloxy group, a substitutable alkynyl carbonyl group, a substitutable alkynyl carbonyloxy group, a substitutable cycloalkoxycarbonyl group, a substitutable cycloalkyl carbonyl group, a substitutable cycloalkyl carbonyloxy group, a substitutable cycloalkenyloxy carbonyl group, a substitutable cycloalkenylic carbonyl group, a substitutable cycloalkenylic carbonyloxy group, a substitutable aryl group, a substitutable aryloxy group, a substitutable arylthio group, a substitutable aryloxycarbonyl group, a substitutable aryl carbonyl group, a substitutable aryl carbonyloxy group, a substitutable heterocyclic group, a substitutable heterocyclyloxy group, a substitutable heterocyclithio group, a substitutable heterocyclyloxy carbonyl group, a substitutable heterocyclyl carbonyl group, a substitutable heterocyclyl carbonyloxy group, a substitutable amino group, a cyano group, a nitro group, a carboxyl group, a substitutable aminocarbonyl group, a substitutable alkylsulfonyl group, a substitutable alkenylsulfonyl group, a substitutable alkynylsulfonyl group, a substitutable cycloalkylsulfonyl group, a substitutable cycloalkenylsulfonyl group, a substitutable arylsulfonyl group, a substitutable heterocyclylsulfonyl group or a substitutable aminosulfonyl group. The number of such substituents may be one or two or more, and such substituents may be the same or different.

[0018] The secondary substituent of the amino group which may be substituted represented by each of R¹, R² and Q, may, for example, be a hydroxyl group, a substitutable alkyl group, a substitutable alkenyl group, a substitutable alkynyl group, a substitutable alkoxy group, a substitutable alkenyloxy group, a substitutable alkynyoxy group, a substitutable cycloalkyl group, a substitutable cycloalkenyl group, a substitutable cycloalkoxy group, a substitutable cycloalkenyloxy group, a substitutable alkoxy carbonyl group, a substitutable alkyl carbonyl group, a substitutable alkenyloxy carbonyl group, a substitutable alkenyl carbonyl group, a substitutable alkynyoxy carbonyl group, a substitutable alkynyl carbonyl group, a substitutable cycloalkoxycarbonyl group, a substitutable cycloalkyl carbonyl group, a substitutable cycloalkenyloxy carbonyl group, a substitutable cycloalkenyl carbonyl group, a substitutable aryl group, a substitutable aryloxy group, a substitutable aryloxycarbonyl group, a substitutable aryl carbonyl group, a substitutable heterocyclic group, a substitutable heterocyclyloxy group, a substitutable heterocyclyloxycarbonyl group, a substitutable heterocyclyl carbonyl group, a substitutable aminocarbonyl group, a substitutable alkylsulfonyl group, a substitutable alkenylsulfonyl group, a substitutable alkynylsulfonyl group, a substitutable cycloalkylsulfonyl group, a substitutable cycloalkenylsulfonyl group, a substitutable arylsulfonyl group, a substitutable heterocyclylsulfonyl group or a substitutable aminosulfonyl group. The number of such secondary substituents may be one or two or more, and such secondary substituents may be the same or different. Further, the two secondary substituents may form a ring containing or not containing a heteroatom.

[0019] The tertiary substituent of each of substitutable groups among the above secondary substituents may, for example, be a halogen atom, a hydroxyl group, a mercapto group, a cyano group, a nitro group, a carboxyl group, an amino group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkenyl group, an aryl group, a heterocyclic group, an alkoxy group, an alkenyloxy group, an alkynyoxy group, a cycloalkyloxy group, a cycloalkenoxy group, an aryloxy group, a heterocyclyoxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenythio group, an arylthio group, a heterocyclythio group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, an arylsulfonyl group, a heterocyclsulfonyl group, an alkylcarbonyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenykarbonyl group, an arylcarbonyl group, a heterocyclkarbonyl group, an alkylloxycarbonyl group, an alkenyloxycarbonyl group, an alkynyoxy carbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, an arylloxycarbonyl group, an arylaminocarbonyl group, an alkylaminocarbonyl group, a dialkylaminocarbonyl group, an alkenylaminocarbonyl group, an alkynylaminocarbonyl group, a cycloalkylaminocarbonyl group, a cycloalkenylaminocarbonyl group, an arylaminocarbonyl group, a heterocyclaminocarbonyl group, an aminosulfonyl group, an alkylaminosulfonyl group, a dialkylaminosulfonyl group, an alkylaminosulfonyl group, an alkynylaminosulfonyl group, a cycloalkylaminosulfonyl group, a cycloalkenylaminosulfonyl group, an arylaminosulfonyl group, a heterocyclaminosulfonyl group, an alkylamino group, a dialkylamino group, an alkylamino group, an alkynylamino group, a cycloalkylamino group, a cycloalkenylamino group, an arylamino group, a heterocyclamino group, an alkylcarbonylamino group, an alkenylcarbonylamino group, an alkynylcarbonylamino group, a cycloalkylcarbonylamino group, a cycloalkenylcarbonylamino group, an arylcarbonylamino group, a heterocyclcarbonylamino group, an alkylsulfonylamino group, an alkenylsulfonylamino group, an alkynylsulfonylamino group, a cycloalkylsulfonylamino group, a cycloalkenylsulfonylamino group, an arylsulfonylamino group or a heterocyclsulfonylamino group. The number of such tertiary substituents may be one or two or more, and when the number is two or more, such substituents may be the same or different. Further, when the secondary substituent is an amino group substituted with two tertiary substituents, such tertiary substituents together may form a ring containing or not containing a heteroatom.

[0020] Further, each of the alkyl moiety, the alkenyl moiety, the alkynyl moiety, the cycloalkyl moiety, the cycloalkenyl

moiety, the aryl moiety and the heterocyclic moiety of each of such tertiary substituents may further be substituted with a quaternary substituent such as a halogen atom, a hydroxyl group, a mercapto group, a cyano group, a nitro group, a carboxyl group, an amino group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylthio group, a haloalkylthio group, an alkoxy carbonyl group, an aminocarbonyl group, an alkylaminocarbonyl group, a di-
5 alkylaminocarbonyl group, an aminosulfonyl group, an alkylaminosulfonyl group, a dialkylaminosulfonyl group, an alkylamino group, a dialkylamino group, an alkylcarbonylamino group, an alkylsulfonylamino group, a cycloalkyl group, an aryl group or a heterocyclic group. The number of such substituents may be one or two or more, and when the number of the substituents is two or more, such substituents may be the same or different.

10 BEST MODE FOR CARRYING OUT THE INVENTION

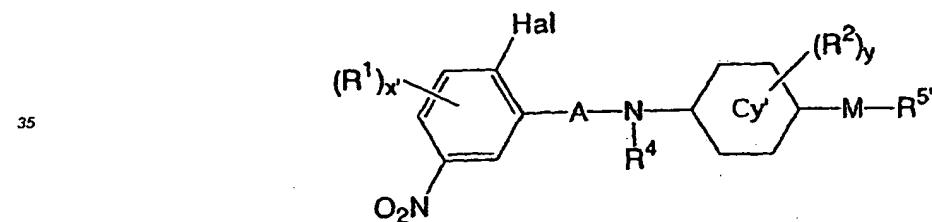
[0021] Now, some of preferred embodiments of the present invention will be explained, however, the present invention is by no means restricted thereto.

[0022] The compounds of the above formula (I) are compounds useful as an active ingredient of cytokine production inhibitors, and are useful as preventive or therapeutic medicines for diseases accompanied by hyperactivated immune functions as listed below.

- (1) At least one type of allergic diseases selected from urticaria, food allergy, anaphylactic shock, hypereosinophilic syndrome, asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis.
- 20 (2) Systemic autoimmune diseases in which antibody production or humoral immunity is hyperactivated.
- (3) At least one type of organ specific autoimmune diseases selected from chronic rheumatoid arthritis, type I diabetes, Hashimoto's thyroiditis, myasthenia gravis and multiple sclerosis.
- (4) Graft rejection accompanying organ transplantation.

[0023] Among the compounds of the above formula (I) and salts thereof, compounds wherein Cy is a phenyl group or a six-membered monocyclic heterocyclic group or salts thereof are preferred as an active ingredient of the cytokine production inhibitors, and among them, more preferred compounds are listed below.

30 (1) Aniline derivatives of the formula (I') or salts thereof:



40 [wherein A, R¹, R², R⁴ and y are as defined above; Hal is a halogen atom; Cy' is a phenyl group or a 6-membered monocyclic heterocyclic group; M is O, S, a NR⁶ group (wherein R⁶ is as defined above), -OCH₂-, -OCH₂CH₂-, -CH₂O-, -CH₂CH₂O-, -SCH₂-, -SCH₂CH₂-, -CH₂S-, -CH₂CH₂S- or a single bond; R⁵ is a pyridyl group which may be substituted or an adamantyl group which may be substituted; and x' is an integer of from 0 to 3; provided that a case where A is CO, and R⁵ is an adamantyl group substituted with a -(CR^aR^a)_d-NCR^bR^c group (wherein R^a is a hydrogen atom or an alkyl group; R^b is a hydrogen atom, an alkyl group or an acyl group, R^c is a hydrogen atom or an alkyl group, and d is an integer of from 0 to 3) is excluded].

45 (2) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO.

(3) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO, and R⁵ is a pyridyl group which may be substituted.

50 (4) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO, and R⁵ is a pyridyl group substituted with a haloalkyl group (provided that the pyridyl group may be substituted with at least one substituent selected from the group consisting of a halogen atom, a hydroxyl group, a mercapto group, a substitutable alkyl group, a substitutable alkenyl group, a substitutable alkynyl group, a substitutable alkoxy group, a substitutable alkylthio group, a substitutable alkenylthio group, a substitutable alkynylthio group, a substitutable cycloalkyl group, a substitutable cycloalkenyl group, a substitutable cycloalkoxy group, a substitutable cycloalkylthio group, a substitutable cycloalkenyloxy group, a substitutable cycloalkenylthio group, a substitutable alkoxy carbonyl group, a substitutable alkylcarbonyl group, a substitutable

alkylcarbonyloxy group, a substitutable alkenyloxycarbonyl group, a substitutable alkenylcarbonyl group, a substitutable alkenylcarbonyloxy group, a substitutable alkynyloxycarbonyl group, a substitutable alkynylcarbonyl group, a substitutable alkynylcarbonyloxy group, a substitutable cycloalkoxycarbonyl group, a substitutable cycloalkylcarbonyl group, a substitutable cycloalkenylcarbonyloxy group, a substitutable cycloalkenylcarbonyl group, a substitutable aryl group, a substitutable aryloxy group, a substitutable arylthio group, a substitutable aryloxycarbonyl group, a substitutable arylcarbonyl group, a substitutable arylcarbonyloxy group, a substitutable heterocyclic group, a substitutable heterocyclyloxy group, a substitutable heterocyclylthio group, a substitutable heterocyclyloxycarbonyl group, a substitutable heterocyclylcarbonyl group, a substitutable heterocyclylcarbonyloxy group, a substitutable amino group, a cyano group, a nitro group, a carboxyl group, a substitutable aminocarbonyl group, a substitutable alkylsulfonyl group, a substitutable alkenylsulfonyl group, a substitutable alkynylsulfonyl group, a substitutable cycloalkylsulfonyl group, a substitutable cycloalkenylsulfonyl group, a substitutable arylsulfonyl group, a substitutable heterocyclylsulfonyl group and a substitutable aminosulfonyl group).

(5) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO, R^{5'} is a pyridyl group substituted with a haloalkyl group, and the pyridyl group may further be substituted with at least one halogen atom.

(6) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO, and R^{5'} is a 3-chloro-5-trifluoromethyl-2-pyridyl group.

(7) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO, and R^{5'} is an adamantyl group which may be substituted.

(8) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO; Hal is a chlorine atom; and R^{5'} is an adamantyl group which may be substituted.

(9) The aniline derivatives of the formula (I') or salts thereof, wherein A is CO; Hal is a fluorine atom, a bromine atom or an iodine atom; and R^{5'} is an adamantyl group which may be substituted.

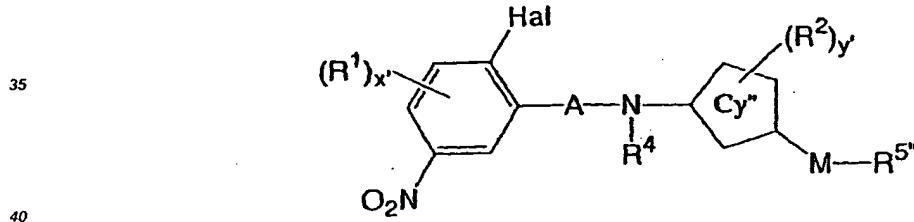
(10) The aniline derivatives of the formula (I') or salts thereof, wherein A is SO₃⁻.

(11) The aniline derivatives of the formula (I') or salts thereof, wherein the 6-membered monocyclic heterocyclic group represented by Cy" is a 6-membered heteroaryl group.

(12) The aniline derivatives or salts thereof as defined in (11), wherein the 6-membered heteroaryl group is a pyridyl group, a pyrimidinyl group, a pyridazinyl group or a pyrazinyl group.

(13) The aniline derivatives of the formula (I") or salts thereof:

30

35
40

[wherein A, R¹, R², R⁴, Hal, M and x' are as defined above; Cy" is a 5-membered monocyclic heterocyclic group; R^{5'} is a phenyl group which may be substituted, a pyridyl group which may be substituted or an adamantyl group which may be substituted; and y' is an integer of from 0 to 3].

- (14) The aniline derivatives of the formula (I") or salts thereof, wherein A is CO.
- (15) The aniline derivatives of the formula (I") or salts thereof, wherein A is CO, and R^{5''} is a phenyl group which may be substituted or a pyridyl group which may be substituted.
- (16) The aniline derivatives of the formula (I") or salts thereof, wherein A is CO, and R^{5''} is an adamantyl group which may be substituted.
- (17) The aniline derivatives of the formula (I") or salts thereof, wherein A is CO, M is an oxygen atom, a sulfur atom or a NR⁶ group (wherein R⁶ is as defined in Claim 1); and R^{5''} is a pyridyl group which may be substituted or an adamantyl group which may be substituted.
- (18) The aniline derivatives of the formula (I") or salts thereof, wherein A is SO₂.
- (19) The aniline derivatives of the formula (I") or salts thereof, wherein the 5-membered monocyclic heterocyclic group represented by Cy" is a 5-membered heteroaryl group.
- (20) The aniline derivatives or salts thereof as defined in (19) wherein the 5-membered heteroaryl group is a furanyl group, a thiienyl group, an imidazolyl group, an oxazolyl group, a pyrrolyl group, an oxadiazolyl group, a thiadiazolyl

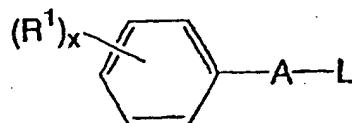
group or a thiazolyl group.

[0024] The compounds of the above formula (I) and salts thereof can be produced by a process for producing known analogous compounds, or a method in accordance therewith, and as preferred embodiments, the following Preparation Methods [1] and [2] will be exemplified.

[1] Preparation Method 1

[0025] A method for producing the aniline derivative of the above formula (I) or a salt thereof, by reacting a compound of the formula (IV):

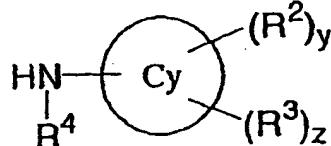
15



20

[wherein A, R¹ and x are as defined above, and L is a leaving group] with a compound of the formula (V):

25



30

[wherein Cy, R², R³, R⁴, y and z are as defined above]. As the leaving group represented by L may, for example, be a halogen atom.

[0026] The reaction of the Preparation Method 1 may be carried out in the presence of a proper solvent. The specific solvent used may, for example, be an aromatic hydrocarbon such as benzene, toluene or xylene; an aliphatic hydrocarbon such as pentane, hexane, heptane, petroleum ether, ligroin or petroleum benzine; an ether such as diethyl ether, dipropyl ether, dibutyl ether, tetrahydrofuran or dioxane; a nitrile such as acetonitrile or propionitrile; an acid amide such as dimethylformamide or dimethylacetamide; a sulfoxide such as dimethylsulfoxide; a sulfone such as sulfolane; a phosphate amide such as hexamethylphosphoramide; or a halogenated hydrocarbon such as chloroform, dichloromethane, carbon tetrachloride or 1,2-dichloroethane, or a mixed solvent thereof.

[0027] In the Preparation Method 1, the reaction is carried out preferably in the presence of a base in some cases. The specific base used may, for example, be an organic base such as triethylamine, pyridine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]-7-undecene or N,N-dimethylaniline; an alkali metal such as lithium, sodium or potassium; a carbonate of an alkali metal such as lithium carbonate, sodium carbonate or potassium carbonate; a hydrogencarbonate of an alkali metal such as lithium hydrogencarbonate, sodium hydrogencarbonate or potassium hydrogencarbonate; a hydride of an alkali metal such as lithium hydride, sodium hydride or potassium hydride; or n-butyllithium, lithium diisopropylamide or sodium amide.

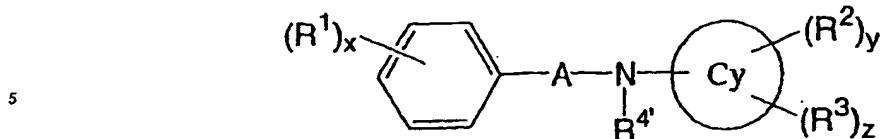
[0028] The reaction of the Preparation Method 1 is carried out usually at a reaction temperature of from -70 to 150°C, preferably at a reaction temperature of from -10 to 100°C. The reaction time is usually from 0.1 to 48 hours.

[0029] In the Preparation Method 1, the compound of the formula (III) may be used in an amount of from 0.8 to 2 equivalents, preferably from 1 to 1.5 equivalents, per 1 mol of the compound of the above formula (II).

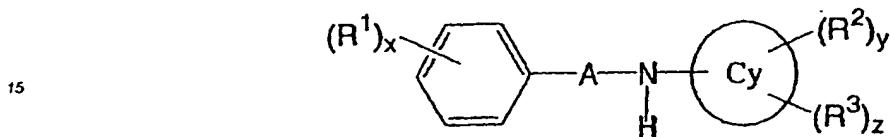
[0030] In the Preparation Method 1, various reaction conditions may optionally be combined with one another. Further, such various reaction conditions include reaction conditions in a usual range and reaction conditions in a preferred range, and they may also be optionally selected and combined with one another.

[2] Preparation Method 2

[0031] A method for producing an aniline derivative of the formula (I-2):



10 [wherein A, Cy, R¹, R², R³, R⁴', x, y and z are as defined above], by reacting a compound of the formula (I-1):



20 [wherein A, Cy, R¹, R², R³, x, y and z are as defined above] with a compound of the formula (VI): R⁴'-L [wherein R⁴' is an alkyl group which may be substituted, and L is as defined above].

[0032] The reaction of the Preparation Method 2 may be carried out in the presence of a proper solvent. The specific solvent used may, for example, be an aromatic hydrocarbon such as benzene, toluene or xylene; an aliphatic hydrocarbon such as pentane, hexane, heptane, petroleum ether, ligroin or petroleum benzine; an ether such as diethyl ether, dipropyl ether, dibutyl ether, tetrahydrofuran or dioxane; a nitrile such as acetonitrile or propionitrile; an acid amide such as dimethylformamide or dimethylacetamide; a sulfoxide such as dimethylsulfoxide; a sulfone such as sulfolane; a phosphate amide such as hexamethylphosphoramide; or a halogenated hydrocarbon such as chloroform, dichloromethane, carbon tetrachloride or 1,2-dichloroethane, or a mixed solvent thereof.

[0033] In the Preparation Method 2, the reaction is carried out preferably in the presence of a base, so as to carry out the reaction efficiently. The specific base used may, for example, be an organic base such as triethylamine, pyridine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]-7-undecene or N,N-dimethylaniline; an alkali metal such as lithium, sodium or potassium; a carbonate of an alkali metal such as lithium carbonate, sodium carbonate or potassium carbonate; a hydrogencarbonate of an alkali metal such as lithium hydrogencarbonate, sodium hydrogencarbonate or potassium hydrogencarbonate; a hydride of an alkali metal such as lithium hydride, sodium hydride or potassium hydride; or n-butyllithium, lithium diisopropylamide or sodium amide.

[0034] The reaction of the Preparation Method 2 is carried out usually at a reaction temperature of from -70 to 150°C, preferably at a reaction temperature of from -10 to 100°C. The reaction time is usually from 0.1 to 48 hours.

[0035] In the Preparation Method 2, the compound of the formula (IV) may be used in an amount of from 0.8 to 2 equivalents, preferably from 1 to 1.5 equivalents, per 1 mol of the compound of the above formula (I-1).

[0036] In the Preparation Method 2, various reaction conditions may optionally be combined with one another. Further, such various reaction conditions include reaction conditions in a usual range and reaction conditions in a preferred range, and they may also be optionally selected and combined with one another.

[0037] The compounds of the above formula (I) obtained by each of the above Preparation Methods 1 and 2 and methods in accordance therewith, may be isolated and purified by means of a known method such as concentration, concentration under reduced pressure, distillation, fractionation, redistribution, solvent extraction, crystallization, recrystallization or chromatography.

[0038] In a case where the compound of the above formula (I) is obtained as a free form, a salt may be formed by a conventional method. Further, the compound of the above formula (I) or a salt thereof or a stereoisomer thereof has a cytokine production inhibitory effect by itself or as mixed.

[0039] Among the compounds of the above formula (I) and salts thereof, the compounds of the formula (I) and salts thereof may be produced by the following Preparation Method [A] or [B] or a combination of these Preparation Methods, in accordance with the above Preparation Method 1 and 2.

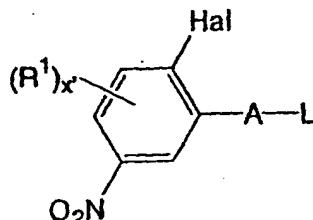
EP 1 344 525 A1

[A] A method for producing the aniline derivative of the above formula (I') or a salt thereof, by reacting a compound of the formula (II):

[0040]

5

10

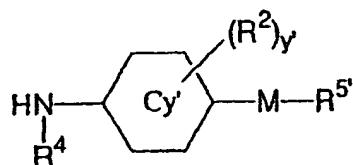


15

[wherein A, R¹, Hal and x' are as defined above, and L is a leaving group] with a compound of the formula (III):

20

25



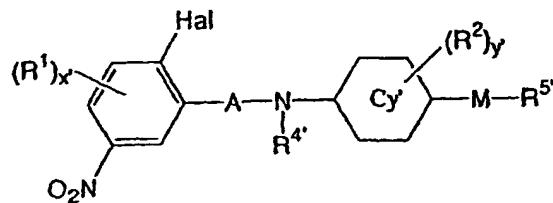
[wherein Cy', R², R⁴, R⁵, M and y' are as defined above]. The Preparation Method [A] is in accordance with the Preparation Method 1, and reaction conditions in the Preparation Method 1 can be applied.

30 [B] A method for producing an aniline derivative of the formula (I'-2) or a salt thereof:

[0041]

35

40

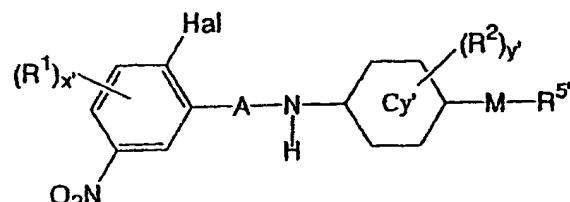


45

[wherein A, Cy', Hal, R¹, R², R⁴', R⁵', M, x' and y' are as defined above], by reacting a compound of the formula (I'-1):

50

55



[wherein A, Cy', Hal, R¹, R², R⁵, M, x' and y' are as defined above] with a compound of the formula (VI): R⁴'-L [wherein R⁴' is an alkyl group which may be substituted, and L is as defined above].

- [0042] The Preparation Method [B] is in accordance with the Preparation Method 2, and reaction conditions in the Preparation Method 2 can be applied.
- [0043] The compounds of the formula [I] of the present invention are usually used in the form of a common pharmaceutical preparation (such as a method as defined in the Japanese Pharmacopoeia Twelfth Edition). The pharmaceutical preparation is prepared by using a commonly used diluent or excipient such as a bulking agent, an extender, a binding agent, a moisture-imparting agent, a disintegrator, a surfactant or a lubricant. As the pharmaceutical preparation, various forms may be selected depending upon the purpose of treatment, and a tablet, a pill, a powder, a dust, a granule, a capsule, a suppository, a solution, a suspension, an emulsion, an injection (such as a solution or a suspension), a spray, an aerosol, a cream, an ointment, a lotion or a transdermal agent (a patch, a matrix or a tape) may be mentioned as examples.
- [0044] To form the medicine into a tablet, carriers which have conventionally been known in this field can be used widely, and they may, for example, be excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid, binding agents such as water, ethanol, propanol, simple syrup, a glucose solution, a starch solution, a gelatin solution, carboxymethyl cellulose, Shellac, methyl cellulose, potassium phosphate and polyvinyl pyrrolidone, disintegrators such as dried starch, sodium alginate, an agar powder, a laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceryl stearate, starch and lactose, disintegration inhibitors such as sucrose, stearin, cacao butter and hydrogenated oil, absorption stimulators such as a quaternary ammonium base and sodium lauryl sulfate, moisturizers such as glycerin and starch, absorbents such as starch, lactose, kaolin, bentonite and colloidal silicate, and lubricants such as purified talc, a stearate, a boric acid powder and polyethylene glycol. Further, a tablet may be a tablet having a common coating applied thereto as the case requires, such as a sugar-coated tablet, a gelatin-coated tablet, an enteric-coated tablet or a film-coated tablet, or a double tablet or a multilayer tablet.
- [0045] To form the medicine into a pill, carriers which have conventionally been known in this field can be used widely, and they may, for example, be excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin and talc, binding agents such as powdered acacia, powdered tragacanth, gelatin and ethanol and disintegrators such as laminaran agar.
- [0046] To form the medicine into a suppository, conventionally known carriers can be used widely, and they may, for example, be polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin and semi-synthetic glyceride.
- [0047] To prepare an injection, a solution, an emulsion or a suspension is sterilized, and is preferably isotonic with the blood, and to form the medicine into a solution, an emulsion or a suspension, all the diluents which are commonly used in this field can be used, and they may, for example, be water, a lactic acid aqueous solution, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. In this case, sodium chloride salt, glucose or glycerin in an amount adequate to prepare an isotonic solution may be incorporated in the pharmaceutical preparation, and a common solubilizing agent, buffer, soothing agent or the like may be added thereto. Further, as the case requires, a colorant, a preservative, a fragrant material, a flavoring agent, a sweetener or another pharmaceutical agent may be incorporated in the pharmaceutical preparation.
- [0048] The amount of the compound of the formula (I) of the present invention is not particularly limited and may optionally be selected from a wide range, but it is usually from 1 to 70 wt%, preferably from 5 to 50 wt% in the entire composition.
- [0049] The administration method of the compounds of the formula (I) of the present invention is not particularly limited, and they are orally or parenterally administered by a method depending upon the form of the preparation, the age, the sex or other conditions of the patient and the degree of the disease. For example, for oral administration, a tablet, a pill, a solution, a suspension, an emulsion, a granule or a capsule may, for example, be mentioned as a preferred form. For parenteral administration, the medicine may be administered in the form of e.g. a topical agent, an injection, a transdermal agent, nasal drops, an inhalant or a suppository. In the case of an injection, it is preferred that the medicine is intravenously administered by itself or as mixed with a conventional fluid replacement such as glucose or amino acids, or as the case requires, it is intramuscularly, intradermally, subcutaneously or intraperitoneally administered by itself. Further, in the case of a suppository, it is preferred that the medicine is administered in rectum.
- [0050] The dose of the compound of the formula (I) of the present invention is optionally selected depending upon e.g. the dose regimen, the age, the sex or other conditions of the patient and the degree of disease, and usually the amount of the compound of the above formula (I) as an active ingredient is preferably from about 0.05 to about 50 mg per kg of the body weight per day, and the medicine may be administered once or several times a day. Further, it is preferred that the active ingredient is contained in an amount of from 1 to 1,000 mg in the administration unit form.

55 EXAMPLES

[0051] Now, Examples (Preparation Examples and Test Examples) of the present invention will be described, how-

ever, the present invention is by no means restricted thereto.

Preparation Example 1

5 Preparation of N-(4-phenoxyphenyl)-2-chloro-5-nitrobenzamide (Compound No. 27)

[0052] Into 5 mL of a tetrahydrofuran solution comprising 420 mg of 4-phenoxyaniline and 250 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 500 mg of 2-chloro-5-nitrobenzoylchloride was dropwise added under cooling with ice. After stirring for about 30 minutes, water was added thereto, and precipitated crystals were collected by filtration. The collected crystals were washed with water and then dried to obtain 730 mg of N-(4-phenoxyphenyl)-2-chloro-5-nitrobenzamide (Compound No. 27) having a melting point of 128°C.

Preparation Example 2

15 Preparation of N-(4-(1-adamantyl)-2-methylphenyl)-2-bromo-5-nitrobenzamide (Compound No. 46)

[0053] To 5 mL of a tetrahydrofuran solution comprising 300 mg of 4-(1-adamantyl)-2-methylaniline hydrochloride and 120 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 290 mg of 2-bromo-5-nitrobenzoylchloride was dropwise added under cooling with ice. After stirring for about 30 minutes, water was added thereto, and the precipitated crystals were collected by filtration. The collected crystals were washed with water and then dried to obtain 310 mg of N-(4-(1-adamantyl)-2-methylphenyl)-2-bromo-5-nitrobenzamide (Compound No. 46) having a melting point of 229°C.

Preparation Example 3

25 Preparation of N-(4-(1-adamantyl)-2-methylphenyl)-2-chloro-5-nitrobenzenesulfonamide (Compound No. 48)

[0054] To 5 mL of a tetrahydrofuran solution comprising 250 mg of 4-(1-adamantyl)-2-methylaniline hydrochloride and 200 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 230 mg of 2-chloro-5-nitrobenzenesulfonylchloride was dropwise added, followed by stirring at about 40°C for about 7 hours. After the mixture was left to stand for cooling, water was added thereto, extraction with chloroform, drying over salt cake and concentration under reduced pressure were carried out to obtain crude crystals. The crude crystals were recrystallized from ether to obtain 150 mg of N-(4-(1-adamantyl)-2-methylphenyl)-2-chloro-5-nitrobenzenesulfonamide (Compound No. 48) having a melting point of 238°C.

Preparation Example 4

35 Preparation of N-(4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-3-methylphenyl)-2-chloro-5-nitrobenzamide (Compound No. 106)

[0055] To 5 mL of a tetrahydrofuran solution comprising 670 mg of 4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-3-methylaniline and 270 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 490 mg of 2-chloro-5-nitrobenzoylchloride was dropwise added, followed by stirring for about 30 minutes, and then water was added, and the precipitated crystals were collected by filtration. The collected crystals were washed with water and then dried to obtain 700 mg of N-(4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-3-methylphenyl)-2-chloro-5-nitrobenzamide (Compound No. 106) having a melting point of from 230 to 232°C.

Preparation Example 5

50 Preparation of N-(2-(1-adamantyloxy)-5-pyridyl)-2-chloro-5-nitrobenzamide (Compound No. 123)

[0056] To 5 mL of a tetrahydrofuran solution comprising 290 mg of 5-amino-2-(1-adamantyloxy)pyridine) and 150 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 260 mg of 2-chloro-5-nitrobenzoylchloride was dropwise added, followed by stirring for about 30 minutes, and then water was added, and the precipitated crystals were collected by filtration. The collected crystals were washed with water and then dried to obtain 330 mg of N-(2-(1-adamantyloxy)-5-pyridyl)-2-chloro-5-nitrobenzamide (Compound No. 123) having a melting point of from 98 to 105°C.

Preparation Example 6

Preparation of N-(4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-3-(1-pyrrolyl)phenyl)-2-chloro-5-nitrobenzamide
(Compound No. 127)

- 5 [0057] To 5 mL of a tetrahydrofuran solution comprising 320 mg of 4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-3-(1-pyrrolyl)aniline and 110 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 200 mg of 2-chloro-5-nitrobenzooylchloride was dropwise added, followed by stirring for about 30 minutes, and then water was added, and the precipitated crystals were collected by filtration. The collected crystals were washed with water and then dried to obtain 10 260 mg of N-(4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-3-(1-pyrrolyl)phenyl)-2-chloro-5-nitrobenzamide (Compound No. 127) having a melting point of from 165 to 167°C.

Preparation Example 7

15 Preparation of N-(4-(3-chloro-5-trifluoromethyl-2-pyridylmethoxy)phenyl)-2-chloro-5-nitrobenzamide (Compound
No. 135)

- 20 [0058] To 5 mL of a tetrahydrofuran solution comprising 300 mg of 4-(3-chloro-5-trifluoromethyl-2-pyridylmethoxy)aniline and 120 mg of triethylamine, 5 mL of a tetrahydrofuran solution comprising 220 mg of 2-chloro-5-nitrobenzooylchloride was dropwise added, followed by stirring for about 30 minutes, and then water was added thereto, and the precipitated crystals were collected by filtration. The collected crystals were washed with water and then dried to obtain 380 mg of N-(4-(3-chloro-5-trifluoromethyl-2-pyridylmethoxy)phenyl)-2-chloro-5-nitrobenzamide (Compound No. 135) having a melting point of from 193 to 195°C.

- 25 [0059] Compounds of the above formula (I) produced in Preparation Examples 1 to 7 and by methods in accordance with the above Preparation Methods 1 and 2 are shown in the following Tables 1 to 20.

30

35

40

45

50

55

Table 1

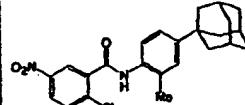
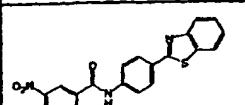
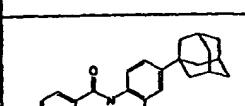
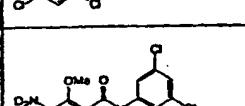
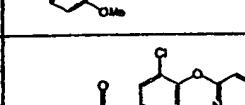
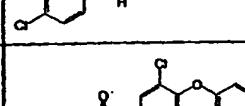
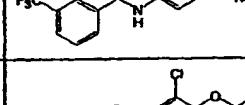
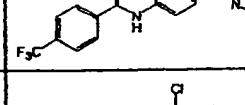
Compound No.	Structural Formula	Physical Properties
1		m.p.: 219°C
2		m.p.: 220-226°C
3		m.p.: 211°C
4		m.p.: 173°C
5		m.p.: 186-188°C
6		m.p.: 160-161°C
7		m.p.: 127-129°C
8		m.p.: 154-155°C
9		m.p.: 152-154°C

Table 2

Compound No.	Structural Formula	Physical Properties
10		m.p.: 103-105°C
11		m.p.: 145-147°C
12		m.p.: 174-176°C
13		m.p.: 141-143°C
14		m.p.: 170-172°C
15		m.p.: 165-167°C
16		m.p.: 176-178°C
17		m.p.: 159-161°C
18		m.p.: 211.5-214.4°C

Table 3

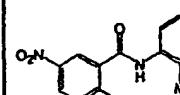
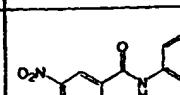
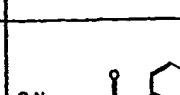
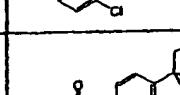
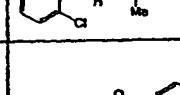
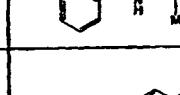
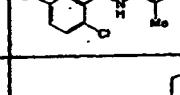
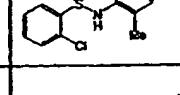
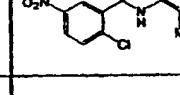
Compound No.	Structural Formula	Physical Properties
19		m.p.: 207°C
20		m.p.: 182°C
21		m.p.: 262°C
22		m.p.: 154°C
23		m.p.: 177°C
24		m.p.: 200°C
25		m.p.: 200°C
26		m.p.: 206°C
27		m.p.: 128°C

Table 4

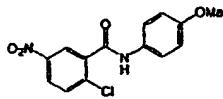
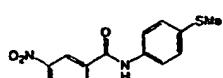
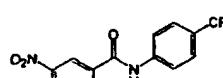
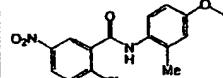
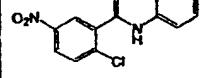
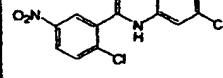
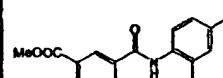
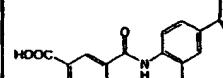
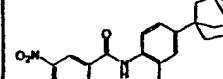
Compound No.	Structural Formula	Physical Properties
28		m.p.: 154°C
29		m.p.: 162°C
30		m.p.: 176°C
31		m.p.: 196°C
32		m.p.: 189°C
33		m.p.: 168°C
34		m.p.: 184°C
35		m.p.: 232°C
36		m.p.: 198°C

Table 5

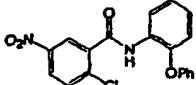
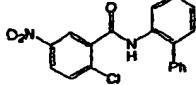
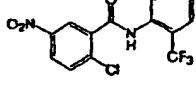
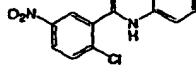
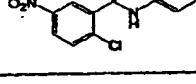
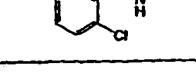
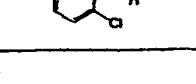
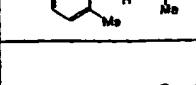
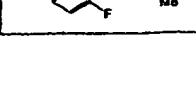
Compound No.	Structural Formula	Physical Properties
37		m.p.: 110°C
38		m.p.: 154°C
39		m.p.: 146°C
40		m.p.: 103°C
41		m.p.: 147°C
42		m.p.: 131°C
43		m.p.: 121°C
44		m.p.: 241°C
45		m.p.: 198°C

Table 6

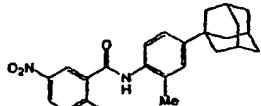
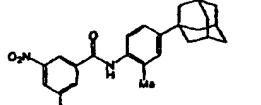
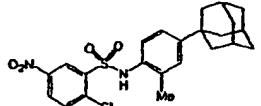
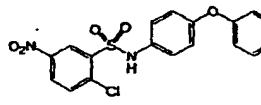
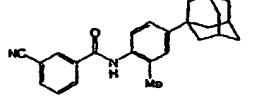
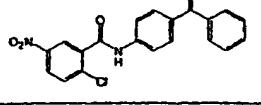
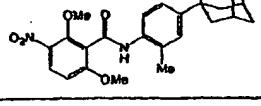
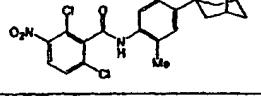
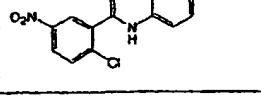
Compound No.	Structural Formula	Physical Properties
46		m.p.: 229°C
47		m.p.: 178°C
48		m.p.: 238°C
49		m.p.: 148°C
50		m.p.: 83°C
51		m.p.: 226°C
52		m.p.: 115°C
53		m.p.: 224°C
54		m.p.: 128°C

Table 7

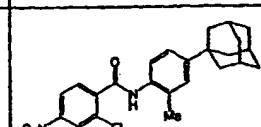
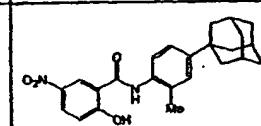
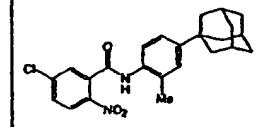
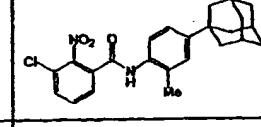
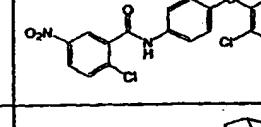
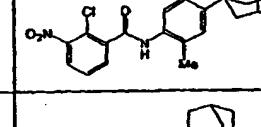
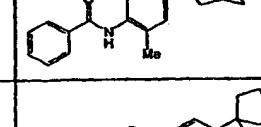
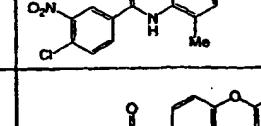
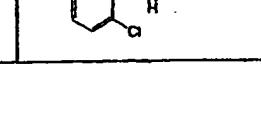
	Compound No.	Structural Formula	Physical Properties
5	55		m.p.: 200°C
10	56		m.p.: 131°C
15	57		m.p.: 233°C
20	58		m.p.: 256°C
25	59		m.p.: 174°C
30	60		m.p.: 222°C
35	61		m.p.: 198°C
40	62		m.p.: 111°C
45	63		m.p.: 198°C
50			

Table 8

Compound No.	Structural Formula	Physical Properties
64		m.p.: 203°C
65		m.p.: 171°C
66		m.p.: 195°C
67		m.p.: 187°C
68		m.p.: 65°C
69		m.p.: 180-183°C
70		m.p.: 69°C
71		m.p.: 168-169°C
72		m.p.: 206-209°C

Table 9

	Compound No.	Structural Formula	Physical Properties
5	73		m.p.: 181-183°C
10	74		m.p.: 289-290°C
15	75		m.p.: 96-100°C
20	76		m.p.: 184-187°C
25	77		m.p.: 176-178°C
30	78		m.p.: 156-157°C
35	79		m.p.: 176-180°C
40	80		m.p.: 171°C
45	81		
50			

Table 10

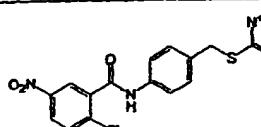
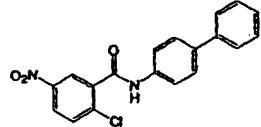
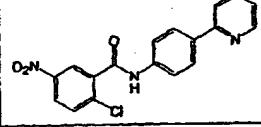
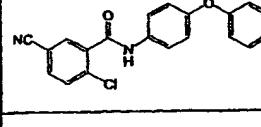
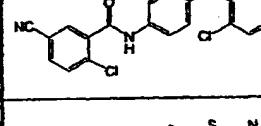
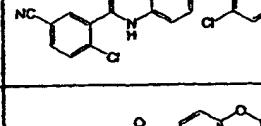
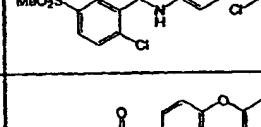
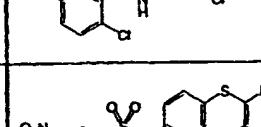
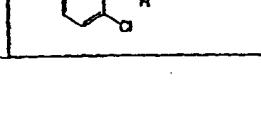
Compound No.	Structural Formula	Physical Properties
82		m.p.: 207-208°C
83		m.p.: 203-206°C
84		
85		m.p.: 143°C
86		m.p.: 209-212°C
87		m.p.: 229-231°C
88		m.p.: 221°C
89		m.p.: 168°C
90		m.p.: 224-226°C

Table 11

	Compound No.	Structural Formula	Physical Properties
5	91		m.p.: 219-221°C
10	92		m.p.: 201-204°C
15	93		m.p.: 224-228°C
20	94		m.p.: 273-275°C
25	95		m.p.: 129-131°C
30	96		m.p.: 167-172°C
35	97		m.p.: 131-134°C
40	98		m.p.: 168-170°C
45	99		m.p.: 191-195°C
50			

Table 12

	Compound No.	Structural Formula	Physical Properties
5	100		m.p.: 154-158°C
10	101		m.p.: 240-245°C
15	102		oily matter
20	103		Amorphous solid
25	104		Amorphous solid
30	105		m.p.: 296-298°C
35	106		m.p.: 230-232°C
40	107		m.p.: 226-229°C
45	108		m.p.: 233-236°C
50			

Table 13

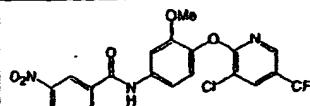
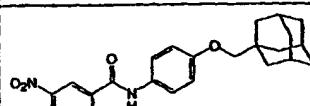
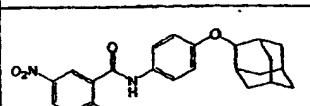
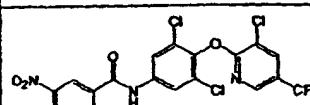
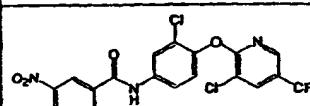
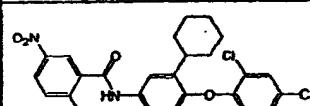
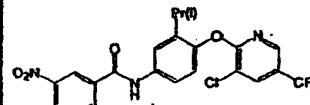
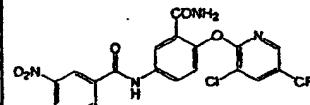
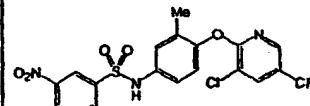
	Compound No.	Structural Formula	Physical Properties
5	109		m.p.: 190-193°C
10	110		m.p.: 175-180°C
15	111		m.p.: 178-180°C
20	112		m.p.: 189-191°C
25	113		m.p.: 222-225°C
30	114		Amorphous solid
35	115		Solid material
40	116		m.p.: 239-244°C
45	117		m.p.: 233-236°C
50			

Table 14

Compound No.	Structural Formula	Physical Properties
118		m.p.: 221-223°C
119		m.p.: 179-181°C
120		m.p.: 246-248°C
121		m.p.: 235-237°C
122		m.p.: 194-198°C
123		m.p.: 98-105°C
124		Amorphous solid
125		m.p.: 203-205°C
126		m.p.: 194-197°C

Table 15

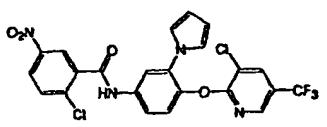
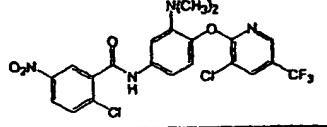
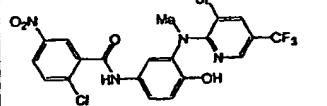
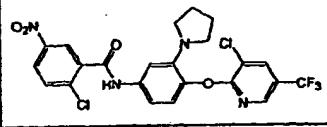
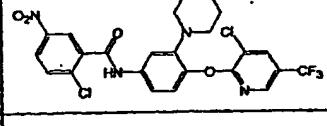
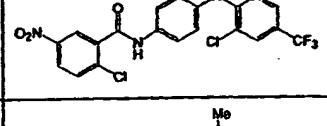
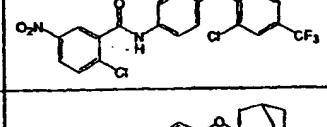
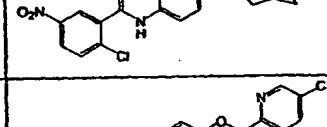
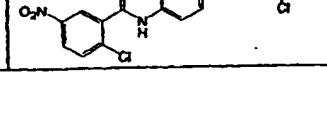
Compound No.	Structural Formula	Physical Properties
127		m.p.: 165-167°C
128		m.p.: 208-213°C
129		m.p.: 273-276°C
130		m.p.: 235-237°C
131		m.p.: 194-198°C
132		m.p.: 215-218°C
133		m.p.: 212-216°C
134		Amorphous solid
135		m.p.: 193-195°C

Table 16

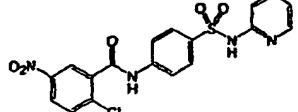
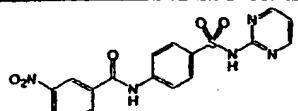
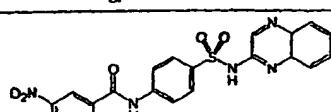
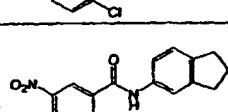
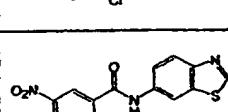
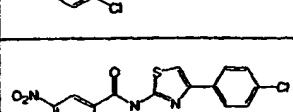
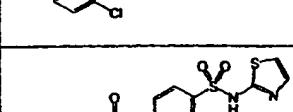
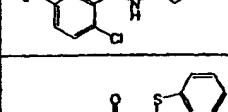
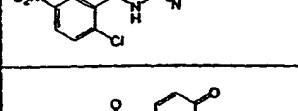
Compound No.	Structural Formula	Physical Properties
136		m.p.: 178-181°C
137		m.p.: 252-258°C
138		m.p.: 146-150°C
139		m.p.: 225-229°C
140		m.p.: 242-244°C
141		m.p.: 217-221°C
142		m.p.: 140-147°C
143		m.p.: 221-227°C
144		m.p.: 116°C

Table 17

Compound No.	Structural Formula	Physical Properties
145		m.p.: 165-172°C
146		m.p.: 235-237°C
147		Amorphous solid
148		m.p.: 189-192°C
149		
150		
151		
152		
153		

Table 18

Compound No.	Structural Formula	Physical Properties
154		
155		
156		
157		
158		
159		
160		
161		
162		

Table 19

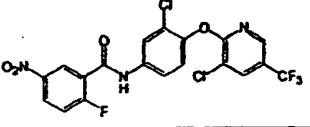
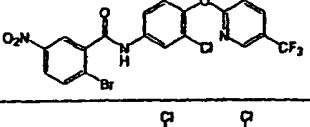
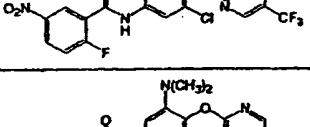
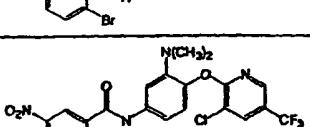
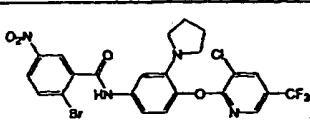
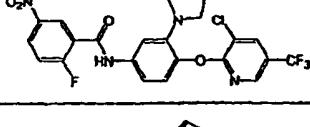
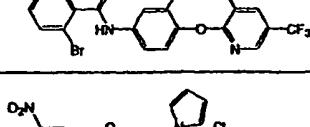
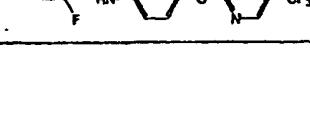
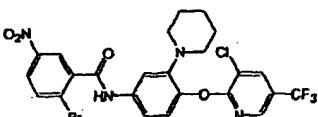
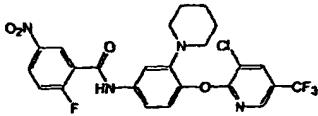
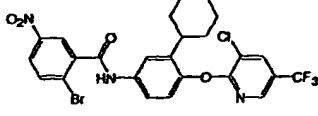
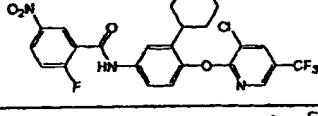
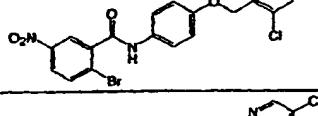
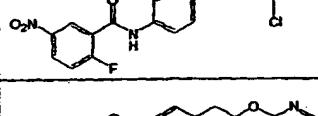
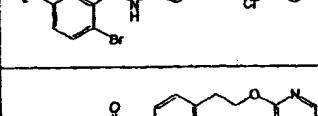
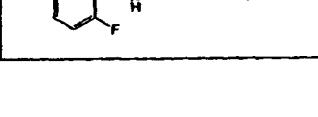
Compound No.	Structural Formula	Physical Properties
163		
164		
165		
166		
167		
168		
169		
170		
171		

Table 20

Compound No.	Structural Formula	Physical Properties
172		
173		
174		
175		
176		
177		
178		
179		

50

55 TEST EXAMPLE (TEST FOR EVALUATION OF CYTOKINE PRODUCTION INHIBITORY EFFECT)

[0060] Murine spleen cells were treated with anti-mouse CD3 antibody and IL-2 to induce cytokine production. The test compounds were added to the cytokine production system to evaluate their inhibitory effect. Namely, anti-mouse

EP 1 344 525 A1

CD3 antibody adjusted to from 10 to 20 µg/ml with borate buffered physiological saline (pH 8.5) was pipetted into a 96-well cell culture plate in an amount of 50 µl/well and left to stand at 4°C for 18 hours. The unreacted solution was removed, washing with Hank's buffer solution was carried out once, and IL-2 adjusted to 10 ng/ml with a RPMI liquid containing 10% fetal bovine serum (FCS) was pipetted in an amount of 50 µl/well. For the negative control group, a solution alone without anti-CD3 antibody nor IL-2 was applied. Then, the diluted solution of each of the test compounds (concentration: 100 ppm unless otherwise specified) was pipetted in an amount of 50 µl/well and a cell suspension of 1×10^7 cells/ml, prepared from spleen of Balb/c mice (female, 7 to 10 week old) was pipetted thereinto in an amount of 100 µl/well. After cultivation in an incubator (37°C, 5% carbon dioxide gas) for from 40 to 48 hours, the culture supernatant was recovered to measure the cytokine production amount by ELISA method.

[0061] With respect to interleukin 5 (IL-5) as a typical Th2 type cytokine and interferon γ (IFN-γ) as a typical Th1 type cytokine, measurements were carried out by the following methods, respectively. Namely, quantitative determination of IL-5 was carried out by the following ELISA method. First, rat anti-mouse IL-5 antibody (Endogen Code No. MM-550C) as a primary antibody was diluted with carbonate buffer solution (pH 9.5) to 1 µg/ml, and spread in a 96 well plate (IWAKI, Code No. 3860-096) in an amount of 50 µl/well for coating at 4°C overnight (16 to 24 hours). Then, the plate was subjected to blocking at 37°C for 2 hours by phosphate buffered physiological saline containing 10% FCS (pH 7.2) (blocking buffer solution) (250 µl/well). The plate was washed with PBS (washing buffer) containing 0.05% Tween 20 (Nacalai Tesque, Code No. 281-51) four times, and a diluted liquid of the culture supernatant was spread in an amount of 50 µl/well, followed by incubation at room temperature for 1 hour. For preparation of a standard line, recombinant mouse IL-5 (R&D systems, Code No. 405-ML) was employed. The plate was washed with a washing buffer four times, and biotin-labeled rat anti-mouse IL-5 antibody (Pharmingen, Code No. 18062D) as a secondary antibody diluted to 0.5 µg/ml with a blocking buffer containing 0.05% Tween 20 was added thereto (50 µl/well), followed by incubation at room temperature for 1 hour. The plate was washed with a washing buffer four times, streptavidin-labeled horseradish peroxidase (Prozyme, Code No. CJ30H001) diluted 800 times with a blocking buffer containing 0.05% Tween 20 was added thereto (50 µl/well), followed by reaction at room temperature for 15 minutes. The plate was washed with a washing buffer four times, and a TNB substrate solution (SIGMA, Code No. T-8665) was added thereto in an amount of 100 µl/well for color developing for from 10 to 20 minutes. A 1M sulfuric acid solution was added thereto in an amount of 100 µl/well to terminate the reaction, and absorption (wavelength 450 nm) was measured by means of micro plate reader (SPECTRA max, Wako Pure Chemicals Industries, Ltd.). Quantitative determination of IFN-γ was carried out in the same manner as the measurement of IL-5, employing rat anti-mouse IFN-γ antibody (Pharmingen, Code No. 18181D) and biotin labeled rat anti-mouse IFN-γ antibody (Pharmingen, Code NO. 18112D), as a primary antibody and a secondary antibody, respectively. For preparation of a standard line, recombinant mouse IFN-γ (GENZYME, Code No. 3485) was employed. The experiment was carried out in duplicate, and the average of the cytokine production amount was obtained. From the average value, the inhibitory ratio (%) was obtained from the following formula, and the results are shown in Tables 21 to 24. With respect to the inhibitory ratio in a case where the concentration of the test compound was not 100 ppm, the concentration of the test compound is shown in () after each inhibitory ratio.

$$\text{Inhibitory ratio (\%)} = \frac{(T-N)}{(P-N)} \times 100$$

40

T: average value of the test compound group, N: average value of the negative control group, and P: average value of the positive control group.

Table 21

No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)	No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)
1	96	90	5	76	83
2	74 (2 ppm)	84 (2 ppm)	6	100	100
3	79	92	7	100	100
4	47	76	8	58 (10 ppm)	67 (10 ppm)

55

EP 1 344 525 A1

Table 22

No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)	No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)
9	96	100	32	99	98
10	100	100	33	100	100
11	37		34	88	97
12	33		35	100	100
13	36		36	81	85
14	46		37	97	100
15	99	100	38	86	93
16	100		39	97	100
17	100	100	40	100	100
18	100	100	41	99	100
19	96	88	42	56	81
20	100	100	43	98	98
21	96	89	44	93	100
22	100	100	45	99	99
23	100	100	46	100	98
24	100		47	89	95
25	89	93	48	100	100
26	82	30	49	100	100
27	96	99	50	95	98
28	100	100	51	99	100
29	98	100	52	75	96
30	100	100	53	94	93
31	62	63	54	62	78

Table 23

No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)	No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)
55	96	100	77	74	50
56	100	100	78	78	91
57	90	98	79	62	90
58	97	96	80	100	100
59	100	100	82	90	99
60	96	93	83	90	76
61	79	89	85	91	86
62	100	100	86	87	29
63	100	100	87	100	100
64	98	99	88	72	17

EP 1 344 525 A1

Table 23 (continued)

No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)	No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)
65	100	100	89	87	99
66	95	91	90	100	100
67	99	100	91	53	1
68	92	99	92	99	100
69	100	100	93	100	100
70	98	99	94	85	53
71	89		95	100	100
72	51		96	100	100
73	64	28	97	77	84
74	43	10	98	96	99
75	100	100	99	100	89
76	96	96	100	92	93

Table 24

No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)	No.	IL-5 production inhibitory ratio (%)	IFN-γ production inhibitory ratio (%)
101	100	100	125	100	100
102	100	100	126	100	100
103	100	100	127	100	100
104	100	100		128 . 96	93
105	55	25	129	86	67
106	83	96	130	100	99
107	99	97	131	100	100
108	100	100	132	99	100
109	100	95	133	99	100
110	99	100	134	97	98
111	99	99	135	62	33
112	100	100	136	98	100
113	96	97	137	98	98
114	100	100	138	99	100
115	100	100	139	89	50
116	100	99	140	100	100
117	100	100	141	100	100
118	78	47	142	95	99
119	100	99	143	97	100
120	84	35	144	99	100
121	97	100	145	100	100

Table 24 (continued)

No.	IL-5 production inhibitory ratio (%)	IFN- γ production inhibitory ratio (%)	No.	IL-5 production inhibitory ratio (%)	IFN- γ production inhibitory ratio (%)
122	100	100	146	62	43
123	100	100	147	99	100
124	100	100	148	94	81

INDUSTRIAL APPLICABILITY

[0062] The present invention provides cytokine production inhibitors useful as preventive or therapeutic medicines for diseases accompanied by hyperactivated immune functions.

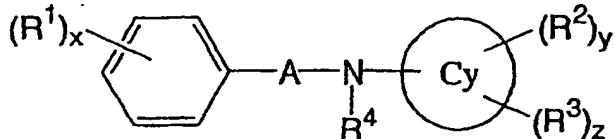
15

Claims

1. A cytokine production inhibitor containing as an active ingredient an aniline derivative of the formula (I) or a salt thereof:

20

25



30

[wherein A is CO or SO₂; Cy is an aryl group or a heterocyclic group; each of R¹ and R² which are independent of each other, is a halogen atom, a cyano group, a nitro group, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted, a heterocyclic group which may be substituted, an amino group which may be substituted or a -B-Q group (wherein B is O, CO, COO, OCO, S, SO or SO₂; and Q is a hydrogen atom, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted, a heterocyclic group which may be substituted or an amino group which may be substituted); R³ is a -M¹-M²-R⁵ group (wherein each of M¹ and M² which are independent of each other, is O, S, a NR⁶ group (wherein R⁶ is a hydrogen atom or an alkyl group which may be substituted), a single bond, a C₁₋₂ alkylene chain, CO, SO or SO₂, or M¹ and M² together may form -N=N-; and R⁵ is a cycloalkyl group which may be substituted, an aryl group which may be substituted or a heterocyclic group which may be substituted); R⁴ is a hydrogen atom or an alkyl group which may be substituted; x is an integer of from 0 to 5; y is an integer of from 0 to 4; and z is an integer of from 0 to 1; provided that (1) a case where Cy is a phenyl group, and the substituent at the 4-position of the phenyl group is a pyrazole group which may be substituted or a triazole group which may be substituted, and (2) a case where Cy is a phenyl group, the substituent at the 2-position of the phenyl group is an alkyl group, and the substituent at the 5-position is a -NHCO-(CH₂)_q-R group (wherein q is an integer of from 1 to 4, and R is an aryl group or a cycloalkyl group) are excluded].

50

2. The cytokine production inhibitor according to Claim 1, wherein Cy is a phenyl group or a six-membered monocyclic heterocyclic group.
3. The cytokine production inhibitor according to Claim 1, wherein the cytokine is Th1 type cytokine.
4. The cytokine production inhibitor according to Claim 1, wherein the cytokine is interferon γ .
5. The cytokine production inhibitor according to Claim 1, wherein the cytokine is Th2 type cytokine.

6. The cytokine production inhibitor according to Claim 1, wherein the cytokine is interleukin 5.
7. A preventive or therapeutic medicine for diseases accompanied by hyperactivated immune functions, which contains the compound or a salt thereof as defined in Claim 1 as an active ingredient.
- 5 8. The preventive or therapeutic medicine according to Claim 7, wherein the disease accompanied by hyperactivated immune functions, is at least one allergic disease selected from urticaria, food allergy, anaphylactic shock, hyper-eosinophilic syndrome, asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis.
- 10 9. The preventive or therapeutic medicine according to Claim 7, wherein the disease accompanied by hyperactivated immune functions is a systemic autoimmune disease.
- 15 10. The preventive or therapeutic medicine according to Claim 9, wherein the disease accompanied by hyperactivated immune functions is at least one organ specific autoimmune disease selected from chronic rheumatoid arthritis, type I diabetes, Hashimoto's thyroiditis, myasthenia gravis and multiple sclerosis.
11. An aniline derivative of the formula (I') or a salt thereof:

20

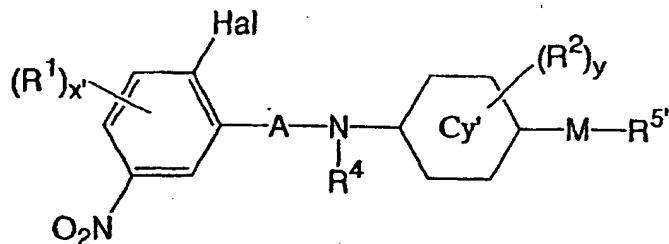
25

30

35

40

45



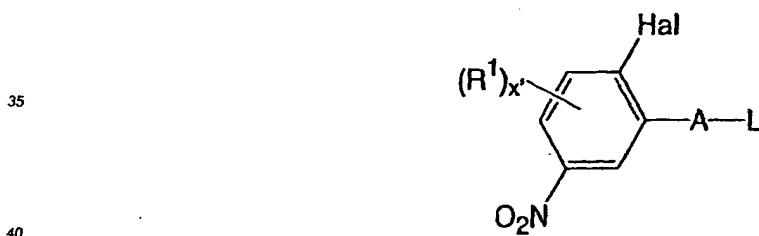
12. The aniline derivative or a salt thereof according to Claim 11, wherein A is CO.

50 13. The aniline derivative or a salt thereof according to Claim 11, wherein A is CO, and R^{5'} is a pyridyl group which may be substituted.

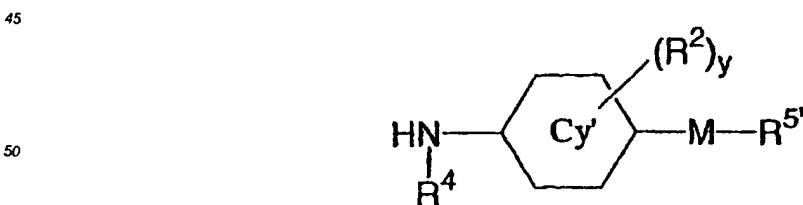
55 14. The aniline derivative or a salt thereof according to Claim 11, wherein A is CO, and R^{5'} is a pyridyl group substituted with a haloalkyl group (provided that the pyridyl group may be substituted with at least one substituent selected from the group consisting of a halogen atom, a hydroxyl group, a mercapto group, a substitutable alkyl group, a substitutable alkenyl group, a substitutable alkynyl group, a substitutable alkoxy group, a substitutable alkylthio group, a substitutable alkenyloxy group, a substitutable alketylthio group, a substitutable alkynylthio group, a substitutable cycloalkyl group, a substitutable cycloalkenyl group, a substitutable

cycloalkoxy group, a substitutable cycloalkylthio group, a substitutable cycloalkenyloxy group, a substitutable cycloalkenylthio group, a substitutable alkoxy carbonyl group, a substitutable alkyl carbonyl group, a substitutable alkyl carbonyloxy group, a substitutable alkenyl carbonyl group, a substitutable alkenyl carbonyloxy group, a substitutable alkynyl carbonyl group, a substitutable alkynyl carbonyloxy group, a substitutable cycloalkoxycarbonyl group, a substitutable cycloalkyl carbonyl group, a substitutable cycloalkyl carbonyloxy group, a substitutable cycloalkenyloxycarbonyl group, a substitutable cycloalkenyl carbonyl group, a substitutable cycloalkenyl carbonyloxy group, a substitutable aryl group, a substitutable aryloxy group, a substitutable arythio group, a substitutable aryloxycarbonyl group, a substitutable aryl carbonyl group, a substitutable aryl carbonyloxy group, a substitutable heterocyclic group, a substitutable heterocyclyloxy group, a substitutable heterocyclylthio group, a substitutable heterocyclyl carbonyl group, a substitutable heterocyclyl carbonyloxy group, a substitutable amino group, a cyano group, a nitro group, a carboxyl group, a substitutable aminocarbonyl group, a substitutable alkylsulfonyl group, a substitutable alkenylsulfonyl group, a substitutable alkynylsulfonyl group, a substitutable cycloalkylsulfonyl group, a substitutable cycloalkenylsulfonyl group, a substitutable arylsulfonyl group, a substitutable heterocyclsulfonyl group and a substitutable aminosulfonyl group).

15. The aniline derivative or a salt thereof according to Claim 11, wherein A is CO, and R^{5'} is a 3-chloro-5-trifluoromethyl-2-pyridyl group.
16. The aniline derivative or a salt thereof according to Claim 11, wherein A is CO, and R^{5'} is an adamantyl group which may be substituted.
17. The aniline derivative or a salt thereof according to Claim 11, wherein A is CO; Hal is a fluorine atom, a bromine atom or an iodine atom; and R^{5'} is an adamantyl group which may be substituted.
18. The aniline derivative or a salt thereof according to Claim 11, wherein A is SO₂.
19. A method for producing the aniline derivative of the above formula (I') or a salt thereof as defined in Claim 11, which comprises reacting a compound of the formula (II):



[wherein A, R¹, Hal and x' are as defined in Claim 11, and L is a leaving group], with a compound of the formula (III):



[wherein Cy', R², R⁴, R^{5'}, M and y are as defined in Claim 11].

55

INTERNATIONAL SEARCH REPORT		International application No. PCT/JP01/11282
A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁷ (See extra sheet.)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁷ (See extra sheet.)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CA (STN), REGISTRY (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Djuric Steven W. et al., "3, 5-Bis(trifluoromethyl) pyrazols: A Novel Class of NFAT Transcription Factor Regulator," Journal of Medicinal Chemistry, Vol.43, No.16 (September 2000) pages 2975 to 2981 (Particularly, Abstract; Table 1,2,3)	1-3,5-10
X	NIWA Satoru et al., "Effect of Am-80, a Retinoid Derivative, on 2, 4-Dinitrofluorobenzene-Induced Contact Dermatitis in Mice," Pharmacology, Vol.60, No.4 (June 2000) pages 208 to 214 (Particularly, Abstract; page 211, left column, line 23 to page 212, right column, line 22)	1-5,7-10
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 27 February, 2002 (27.02.02)		Date of mailing of the international search report 12 March, 2002 (12.03.02)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT		International application No. PCT/JP01/11282
C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP, 1024138, A1 (Yamanouchi Pharmaceutical Co., Ltd.), 02 August, 2000 (02.08.00), (Particularly, Par. No. [0014]; Table 2,3,5) & WO 99/19303 A1 & AU 9887139 A & CN 1218046 A & JP 11-240832 A & HU 9802310 A & KR 99037018 A & BR 9803883 A & NO 200001907 A	1-3,7-10 11-19
X	JP, 10-251144, A (Institute of Medicinal Molecular Design Inc.), 22 September, 1998 (27.09.98), (Family: none) (Particularly, Claims; Par. Nos. [0023] to [0025])	1,2,5,7-10
X	WO, 00/40239, A1 (Smithkline Beecham Corp.), 13 July, 2000 (13.07.00), (Particularly, Claims) & EP 1140072 A1	7-10
PX	WO, 01/83427, A1 (Sankyo Co., Ltd.), 08 November, 2001 (08.11.01), (Family: none) (Particularly, Example 8, 147)	11-19

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11282

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

Int.Cl' A61K31/167, 31/428, 31/44, 31/4402, 31/4439, 31/4545, 31/505, 31/498, 31/428, 31/444, 31/5377, 31/496, 31/5375, C07D277/66, 213/64, 213/70, 213/71, 213/61, 213/76, 213/75, 239/69, 241/44, 277/62, 277/52, 277/82, 213/64, 295/12, A61P43/00, 37/06, 37/08, 17/04, 11/06, 27/16, 27/14, 27/02, 29/00, 19/02, 3/10, 21/04, C07C233/65, 233/75, 235/56, 323/42, 323/62, 317/44, 311/21
(According to International Patent Classification (IPC) or to both national classification and IPC)

Continuation of B. FIELDS SEARCHED
Minimum Documentation searched (International Patent Classification (IPC))

Int.Cl' A61K31/167, 31/428, 31/44, 31/4402, 31/4439, 31/4545, 31/505, 31/498, 31/428, 31/444, 31/5377, 31/496, 31/5375, C07D277/66, 213/64, 213/70, 213/71, 213/61, 213/76, 213/75, 239/69, 241/44, 277/62, 277/52, 277/82, 213/64, 295/12, A61P43/00, 37/06, 37/08, 17/04, 11/06, 27/16, 27/14, 27/02, 29/00, 19/02, 3/10, 21/04, C07C233/65, 233/75, 235/56, 323/42, 323/62, 317/44, 311/21
Minimum documentation searched (classification system followed by classification symbols)

REMARK CONCERNING THE SUBJECT OF SEARCH:

Claims 1-19 relate to a variety of compounds, cytokine production inhibitors containing the compounds as the active ingredient, or preventive or therapeutic drugs for various diseases.

However, only a small part of the compounds and the uses are supported by the description within the meaning of Article 6 of the PCT and disclosed within the meaning of Article 5 of the PCT.

Therefore, this search has been carried out with priority given to the part supported by the description and disclosed therein, that is, to Examples.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.